P1778R1C2

CLAIMS:

1. A compound of the formula I, II or III:

$$X_{2}$$
 X_{3}
 X_{2}
 X_{3}
 X_{2}
 X_{3}
 X_{4}
 X_{2}
 X_{3}
 X_{4}
 X_{2}

$$X_1 O = X_2$$
 $X_1 O = X_2$
 $X_2 O = X_1 O = X_2$

 \mathbf{m}

wherein

Z is H or lower alkyl;

or

A has the structure:

or or

in which

B is cyanoalkyl, a carbocycle or a heterocycle optionally substituted with one or more R₁ substituents;

q is 0-3;

R₁, R₂, R₃, R₄, R₅ and R₆ independently are hydrogen, alkyl, amino, alkylamino, dialkylamino, nitro, urea, cyano, thio, alkylthio, hydroxy, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylamino, aryloxycarbonylamino, alkylsulfinyl, sulfonyl, alkylsulfonyl, aralkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkanoyl, alkanoylamino, cycloalkanoylamino, aryl, arylalkyl, halogen, or alkylphosphonyl, and R₁, R₂, R₃, R₄ and R₅ are substituted with 0-3 substituents selected from the group consisting of hydroxy, carboxyl, lower alkoxycarbonyl, lower alkyl, nitro, oxo, cyano, carbocyclyl, heterocyclyl, heteroaryl, lower alkylthio, lower alkoxy, lower alkylamino, lower alkanoylamino, lower alkylsulfinyl, lower sulfonyl, lower alkylsulfonyl, lower alkanoyl, aryl, aroyl, heterocyclylcarbonyl, halogen and lower alkylphosphonyl; or two of R₁ to R₅ together form a carbocycle or heterocyclic ring;

Y is H, alkoxy, alkoxyalkoxy, aryloxy, alkylaminoalkoxy, dialkylaminoalkoxy, alkylamino, arylamino, heterocyclyl or heteroarylalkyl, where each of the forgoing may be substituted or unsubstituted;

X₁ is H, C(O)OR, C(O)NRaRb, C(O)R, or C(O)SR, wherein R, Ra and Rb, individually, is hydrogen or alkyl, alkoxy, aryl, heterocyclyl, heteroaryl, substituted with 0-4 substituents selected from the group consisting of halogen, hydroxy, amino, carboxyl, nitro, cyano, heterocylyl, heteroaryl, aryl, aroyl, aryloxy, aralkyl, aralkyloxy, aryloxycarbonyl, aralkyloxycarbonyl, alkylenedioxy, lower alkoxycarbonyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkylthio, lower alkoxy, lower alkylamino, lower alkylsulfinyl, lower sulfonyl, lower alkylsulfonyl, lower alkylnyl, aminosulfonyl lower alkyl, hydroxy lower alkyl, alkylsulfinyl lower alkyl, alkylsulfonyl lower alkyl, alkylthio lower alkyl, heteroarylthio lower alkyl, heteroaryloxy lower alkyl, heteroarylamino lower alkyl, halo lower alkyl, and alkoxy lower alkyl; wherein said heterocyclyl, heteroaryl, aryl, aroyl, aryloxy, aralkyl, aralkyloxy, aryloxycarbonyl and aralkyloxycarbonyl is optionally substituted with halogen, hydroxyl, amino, carboxyl, nitro, cyano, alkyl and alkoxy; and wherein Ra and Rb together with the nitrogen to which they are attached may form a heterocyclyl or heteroaryl group substituted with 0-5 substituents R or Rd; wherein Rd has the structure

wherein X' is a divalent linker selected from the group consisting of C(O)NRa, C(O) or a bond;

 X_2 and X_3 are each independently hydrogen, halogen, hydroxy, amino, carboxyl, nitro, cyano, or substituted or unsubstituted alkyl, aryl, heterocylyl, heteroaryl, aryl, aroyl, aryloxy, alkylenedioxy, lower alkyl carbonylamino, lower alkenyl carbonylamino, arylamino, arylamino, lower alkoxy carbonylamino, lower alkylamino carbonylamino, arylamino carbonylamino, lower alkoxycarbonyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkylthio, lower alkoxy, lower alkylamino, lower alkylsulfinyl, lower sulfonyl, lower alkylsulfonyl, lower alkylsulfonyl, lower alkyl, hydroxy lower alkyl, alkylsulfinyl lower alkyl, alkylsulfonyl lower alkyl, alkylthio lower alkyl, heteroarylthio lower alkyl, heteroaryloxy lower alkyl, heteroarylamino lower alkyl, halo lower alkyl, alkoxy lower alkyl; and wherein X_1 and X_2 or X_3 may be bonded together to form a heterocylic or heteroaryl ring(s); or X_3 and Z together form a heterobicyclic ring;

X₁·, X₂·, X₃· and X₄· are each independently hydrogen, halogen, hydroxy, amino, carboxyl, nitro, cyano, or substituted or unsubstituted alkyl, alkenyl, alkynyl, arylalkyl, heterocylyl, heteroaryl, aryl, aroyl, aryloxy, alkylenedioxy, lower alkyl carbonylamino, lower alkenyl carbonylamino, aryl carbonylamino, arylalkyl carbonylamino, lower alkoxy carbonylamino, lower alkylamino carbonylamino, arylamino carbonylamino, lower alkoxycarbonyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkylthio, lower alkoxy, lower alkylamino, lower alkylsulfinyl, lower sulfonyl, lower alkylsulfonyl, lower alkyl, aminosulfonyl lower alkyl, hydroxy lower alkyl, alkylsulfinyl lower alkyl, alkylsulfonyl lower alkyl, heteroarylthio lower alkyl, heteroaryloxy lower alkyl, heteroarylamino lower alkyl, halo lower alkyl, alkoxy lower alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, having the formula:

$$X_1O$$
 X_2
 X_3
 X_4
 X_5
 X_6
 X_6

I

wherein

Z is H or lower alkyl;

A has the structure:

$$R_1$$
 R_2
 R_3

in which R₁, R₂, R₃, R₄ and R₅, independently are hydrogen, alkyl, amino, alkylamino, dialkylamino, nitro, cyano, thio, alkylthio, hydroxy, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkylsulfinyl, sulfonyl, alkylsulfonyl, alkanoyl, aryl, arylalkyl, halogen, or alkylphosphonyl, and R₁, R₂, R₃, R₄ and R₅ are substituted with 0-3 substituents selected from the group consisting of hydroxy, carboxyl, lower alkoxycarbonyl, lower alkyl, nitro, cyano, heterocylyl, heteroaryl, lower alkylthio, lower alkoxy, lower alkylamino, lower alkylsulfinyl, lower sulfonyl, lower alkylsulfonyl, lower alkanoyl, aryl, halogen and lower alkylphosphonyl;

Y is H, alkoxy, alkoxyalkoxy, aryloxy, aminoalkylalkoxy, diaminoalkylalkoxy, alkylamino, arylamino, heterocyclyl or heteroarylalkyl, where each of the forgoing may be substituted or unsubstituted;

X₁ is H, C(O)OR, C(O)NRaRb, C(O)R, or C(O)SR, wherein R, Ra and Rb, individually, is hydrogen or alkyl, aryl, heterocyclyl, heteroaryl, substituted with 0-4 substituents selected from the group consisting of halogen, hydroxy, amino, carboxyl, nitro, cyano, heterocylyl, heteroaryl, aryl, aroyl, aryloxy, alkylenedioxy, lower alkoxycarbonyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkylthio, lower alkoxy, lower alkylamino, lower alkylsulfinyl, lower sulfonyl, lower alkylsulfonyl, lower alkyl, hydroxy lower alkyl, alkylsulfinyl lower alkyl, alkylsulfonyl lower alkyl, alkylthio lower alkyl, heteroarylthio lower alkyl, heteroaryloxy lower alkyl, heteroarylamino lower alkyl, halo lower alkyl, alkoxy lower alkyl; and wherein Ra and Rb together with the nitrogen to which they are attached may form a heterocyclyl or heteroaryl group substituted with 0-4 substituents R;

X₂ and X₃ are each independently hydrogen, halogen, hydroxy, amino, carboxyl, nitro, cyano, or substituted or unsubstituted alkyl, aryl, heterocylyl, heteroaryl, aryl, aroyl, aryloxy, alkylenedioxy, lower alkyl carbonylamino, lower alkenyl carbonylamino, aryl carbonylamino, arylamino, lower alkoxy carbonylamino, lower alkylamino carbonylamino, lower alkoxycarbonyl, lower alkyl, lower alkynyl, lower alkynyl, lower

alkylthio, lower alkoxy, lower alkylamino, lower alkylsulfinyl, lower sulfonyl, lower alkylsulfonyl, lower alkylphosphonyl, aminosulfonyl lower alkyl, hydroxy lower alkyl, alkylsulfinyl lower alkyl, alkylsulfonyl lower alkyl, alkylthio lower alkyl, heteroarylthio lower alkyl, heteroaryloxy lower alkyl, heteroarylamino lower alkyl, halo lower alkyl, alkoxy lower alkyl; and wherein X_1 and X_2 or X_3 may be bonded together to form a heterocylic or heteroaryl ring(s);

or

$$X_2$$
 X_3
 X_4
 Z
 X_1

 \mathbf{II}

wherein

Z is H or lower alkyl;

A has the structure:

in which R₁, R₂, R₃, R₄ and R₅, independently are hydrogen, alkyl, amino, alkylamino, dialkylamino, nitro, cyano, thio, alkylthio, hydroxy, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkylsulfinyl, sulfonyl, alkylsulfonyl, alkanoyl, aryl, arylalkyl, halogen, or alkylphosphonyl, and R₁, R₂, R₃, R₄ and R₅ are substituted with 0-3 substituents selected from the group consisting of hydroxy, carboxyl, lower alkoxycarbonyl, lower alkyl, nitro, cyano, heterocylyl, heteroaryl, lower

alkylthio, lower alkoxy, lower alkylamino, lower alkylsulfinyl, lower sulfonyl, lower alkylsulfonyl, lower alkylsulfonyl, lower alkylphosphonyl;

Y is H, alkoxy, alkoxyalkoxy, aryloxy, aminoalkylalkoxy, diaminoalkylalkoxy, alkylamino, arylamino, heterocyclyl or heteroarylalkyl, where each of the forgoing may be substituted or unsubstituted;

X₁, X₂ and X₃ are each independently hydrogen, halogen, hydroxy, amino, carboxyl, nitro, cyano, or substituted or unsubstituted alkyl, alkenyl, alkynyl, arylalkyl, heterocylyl, heteroaryl, aryl, aroyl, aryloxy, alkylenedioxy, lower alkyl carbonylamino, lower alkenyl carbonylamino, aryl carbonylamino, arylalkyl carbonylamino, lower alkoxy carbonylamino, lower alkylamino carbonylamino, arylamino carbonylamino, lower alkoxycarbonyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkylthio, lower alkoxy, lower alkylamino, lower alkylsulfinyl, lower sulfonyl, lower alkylsulfonyl, lower alkyl, alkylsulfonyl lower alkyl, alkylsulfinyl lower alkyl, alkylsulfonyl lower alkyl, alkylthio lower alkyl, heteroaryloxy lower alkyl, heteroarylamino lower alkyl, halo lower alkyl, alkoxy lower alkyl; or a pharmaceutically acceptable salt thereof.

- 3. The compound of claim 2 having structure I.
- 4. The compound of claim 2, having structure II.
- 5. The compound of one of claims 2, wherein X_1 X_2 , X_3 are each independently H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterocylyl, or heteroaryl.
- 6. The compound of claim 5, wherein X_1 is C(O)OR, C(O)R, or C(O)SR.
- 7. The compound of claim 5, wherein X_1 is C(O)NRaRb.
- 8. The compound of claim 5, wherein X_1 is C(O)NRaRb and wherein Ra and Rb together with the nitrogen to which they are attached form a 5-membered or 6-membered heterocyclyl or heteroaryl group substituted with 0-4 substituents R.

9. The compound of claim 7, wherein X_1 is a member selected from the group consisting of

10. The compound of claim 9, wherein X_1 is

- 11. The compound of claim 7, wherein X_1 is C(O)NRaRb and wherein Ra and Rb are independently hydrogen, substituted or unsubstituted alkyl, aryl, heterocyclyl, or heteroaryl.
- 12. The compound of claim 11, wherein X_1 is a member selected from the group consisting of

- 13. The compound of claim 11, wherein R_1 , R_5 or both are not hydrogen.
- 14. The compound of claim 1, wherein X_2 , X_3 , Z or a combination thereof are hydrogen.
- 15. The compound of claim 1, wherein A is selected from the group consisting of

$$\begin{array}{c} CI + CI \\ + CI \\$$

16. The compound of claim 1, wherein A is

17. The compound of claim 1, wherein X_2 is a member selected from the group consisting of

- 18. The compound of claim 1, wherein the compound has S stereochemical configuration.
- 19. A composition, comprising the compound of claim 1 and a carrier or excipient.
- 20. A medicament, comprising the compound of claim 1 and a therapeutically inert carrier or excipient.
- 21. A medicament for treating a disease or condition associated with binding of alpha4beta7 to MAdCAM-1 or alpha4beta1 to VCAM-1, comprising the compound of claim 1 and a therapeutically inert carrier or excipient.
- 22. A medicament for treating rheumatoid arthritis, asthma, psoriasis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, pouchitis, Crohn's disease, Celiac disease, nontropical Sprue, graft-versus-host disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, pericholangitis, chronic sinusitis, chronic bronchitis, pneumonitis, collagen disease, eczema or systemic lupus erythematosis, comprising the compound of claim 1 and a therapeutically inert carrier or excipient.

- 23. A method for treating a disease or condition associated with binding of alpha4beta7 to MAdCAM-1 or alpha4beta1 to VCAM-1, comprising administering an effective amount of the compound of claim 1 to a mammal in need thereof.
- 24. A method for treating rheumatoid arthritis, asthma, psoriasis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, pouchitis, Crohn's disease, Celiac disease, nontropical Sprue, graft-versus-host disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, pericholangitis, chronic sinusitis, chronic bronchitis, pneumonitis, collagen disease, eczema or systemic lupus erythematosis, comprising administering an effective amount of the compound of claim 1 to a mammal in need thereof.